Docket No.: 85424-0027
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tomoko Nakayama, et al.

Application No.: 09/843,819

Group Art Unit: 1634

Filed: April 30, 2001

Examiner: S. Sakelaris

For: METHOD FOR SYNTHESIS OF NUCLEIC ACIDS

AMENDMENT

Box Non-Fee Amendment
Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Office Action dated September 17, 2002 (Paper No. 7), please amend the above-identified U.S. patent application as follows:

In the Specification

Please amend the Abstract (page 20, lines 2 to 18) as follows:

The present invention is a method for synthesis of nucleic acids to amplify an intended nucleic acid in a region in which a GC content is rich, wherein a polyhydric alcohol and/or ammonium sulfate is present in an amplification reaction solution. According to the present invention, it is possible to amplify nucleic acids in a GC rich region efficiently and directly from a sample such as blood containing lots of PCR inhibitory substances without undergoing a process of isolating and purifying the nucleic acid, even though conducting PCR in the GC rich region tends to be difficult using conventional processes even if purified DNA is used.

In the Claims

Please cancel claim 12. Please further amend the claims as follows.

1. (amended) A method for synthesis of nucleic acids, which comprises:

amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate.

2. (amended) The method for synthesis of nucleic acids according to claim 1, wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution.

3. (amended) The method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

REMARKS/ARGUMENTS

This is a full and timely response to the Office Action dated September 17, 2002. By way of the present amendment, claims 1 to 3 are amended. Claim 12 is canceled, and no claims are added. Thus, claims 1 to 11 are pending for the Examiner's consideration.

In the Action, the Examiner rejected the claims under 35 U.S.C. § 112, second paragraph as containing indefinite language. Particularly, the comments are directed toward claims 1 to 3. The present amendment is believed to overcome these rejections.

The Examiner rejected claims 1 to 2, and 4 to 9 under 35 U.S.C. § 102(b) as being anticipated by Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke"). Claims 1 to 2, and 4 to 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's

Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe"). These rejections are respectfully traversed in light of the present amendment.

The present amendment incorporates the features of claim 12 into claim 1. Neither Henke nor Watanabe teaches or suggests that a polyhydric alcohol and ammonium sulfate are present in an amplification reaction solution together. In fact, it is clear that a person of ordinary skill in the art would not find motivation in the Henke and Watanabe references to combine their teachings to arrive at such an amplification reaction solution.

Henke essentially teaches away from adding a polyhydric alcohol such as glycerine in some PCR solutions, depending on the nucleic acid to be amplified. Henke teaches (p. 3957) that in a co-amplification of both an antigen's mRNA (GC-rich) and a variant of the antigen's mRNA (also GC-rich) by RT and PCR, 10% glycerine proved ineffective at co-amplification. The amplification of the variant of the antigen's mRNA was optimized when glycerine was added, but the amplification of the antigen's mRNA was depressed. The Examiner's position is that even though Henke tends to discourage the use of glycerine in a PCR amplification, it still anticipates the invention as claimed in claim 1, and 4 to 9. Applicant respectfully disagrees with the Examiner, particularly regarding claim 2, as it appears that Henke's PCR process involved isolated gene fragments, and not a more complex nucleic acid inclusion body or an even more complex living body-derived sample. In fact, Watanabe discloses that genomic DNA was extracted from peripheral lymphocytes (page 17, lines 13 to 14).

Watanabe only makes mention of a PCR process at column 1 of page 17, and column 1 of page 18. In these passages, Watanabe discloses that during a PCR process, 10 mM ammonium sulfate is added to the solution that includes blood samples, and that the ammonium sulfate is greatly effective in terms of improving the efficiency of the process. However, Watanabe clearly fails to teach or suggest the feature of a polyhydric alcohol and ammonium sulfate being present in an amplification reaction solution together.

A person of ordinary skill in the art who reads Henke would actually be steered away from trying to perform PCR using glycerine together with another compound such as ammonium sulfate. Henke teaches that glycerine is not effective at co-amplification PCR, and teaches that betaine improves the co-amplification process when used in place of glycerine. Then, from

reading the advantages of using ammonium sulfate in a PCR solution, a person of ordinary skill in the art would, at best, be persuaded to add ammonium sulfate and betaine to a PCR solution for coamplification. However, Watanabe fails to provide any teachings that would overcome a Henke-based presumption that glycerine would be ineffective. When the teachings of the prior art are considered as a whole, there is no motivation found in the references to render the combined claims 1 and 12 obvious.

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Henke in view of Barnes, "PCR Amplification of Up to 35-kb DNA with High Fidelity and High Yield from λ Bacteriophage Templates," 91 PNAS 2216 (1994) ("Barnes"). Barnes teaches that raising the pH in a PCR solution improves the PCR yield when the nucleic acid being amplified is particularly high, i.e., 28 to 35 kb (page 2217, col. 1). The Examiner's position is that given Henke's teachings of a GC rich nucleic acid amplification, it would be suggested to a person of ordinary skill in the art to apply Barnes' teaching of raising the pH in the PCR solution to the Henke process. In any respect, it is clear that Barnes fails to teach or suggest the use of either a polyhydric alcohol or ammonium sulfate in an amplification reaction solution. Therefore, the present amendment is believed to overcome the rejection of claim 3 as well.

Claim 10 is rejected as being unpatentable over Henke in view of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller"). Pomp is provided for its teachings of the use of 5 to 20% ethylene glycol in PCR solutions that only used DMSO as an enhancing agent. Since Henke is directed to PCR solutions that could use DMSO, the Examiner's position is that it would be obvious to combine Henke and Pomp to arrive at claim 10. Further, Fuller is provided for its teachings of the use of between 10 and 50% glycerol or ethylene glycol are added to an amplification solution. In any respect, Pomp and Fuller fail to teach or suggest the use of both ammonium sulfate and a polyhydric alcohol in an amplification reaction solution, as claimed in claim 1 as presently amended.

Finally, claims 3 and 11 are rejected as being unpatentable over Watanabe in view of U.S. Patent No. 5,972,618 ("Bloch"). Bloch is provided for teaching an increased pH and concentration of ammonium sulfate in a PCR solution. Again, Bloch fails to teach or suggest the

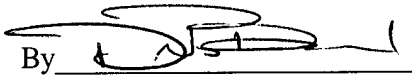
use of both ammonium sulfate and a polyhydric alcohol in an amplification reaction solution. Consequently, the rejections of claims 3 and 11 are believed to be overcome.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Dated: December 17, 2002

Respectfully submitted,



By_____

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